Aspects of the preoperative assessment in patients undergoing liver surgery

Valorization

This chapter is intended to take a brief look upon the return of investment prospects for society form the knowledge gathered during this PhD-trajectory. Every (medical) researcher knows that one of the crucial parts of developing a new technique or treatment is validating experimental data in a human translational model or in the clinical setting. However, when a certain technique or treatment is validated properly this should not be the end of the story. It is important that researchers challenge themselves to translate the gained academic wisdom to societal or economic benefit. This is particularly the case because often taxpayers, charities or foundations have funded the research. The possibilities for future implementation and also the economic and societal value of the findings of this thesis will be discussed.

Liver volumetry

The results from this thesis have contributed to the implementation of liver volumetry in the preoperative assessment of patients undergoing liver surgery. In the Netherlands every year more than 1000 liver resections are performed. Unfortunately, liver volumetric analysis is currently not standard in the preoperative assessment in patients undergoing major liver resection. Collaboration with the (liver) radiologist is key and will become increasingly more important in the future. Radiology will continue to play a central component in the surgical treatment of malignant/benign liver tumours. Radiologists and HPB surgeons should work together in the form of an interdisciplinary interface. At the present time, radiology is faced with the challenge of visualizing more discrete aspects of the liver tumour than size and location, such as tumour necrosis and altered tumour perfusion. In MRI scans newly developed contrast agents are used that are extracted by the liver and which give the opportunity to assess liver function. These developments in radiology will contribute actively to a better understanding of the genesis of malignant disease of the liver and to the improvement of existing surgical therapy regimes. It is all about identifying patients at increased risk of postoperative liver failure after liver resection. Assessing the future remnant liver volume is critical in this context. It was shown by our group that sarcopenia negatively influences total functional liver volume in patients undergoing liver surgery. Sarcopenia could therefore be one of the decisive factors in the risk analysis for postoperative liver failure. This should be studied more thoroughly in the future. For instance it could be studied whether sarcopenia has an effect on hepatocellular damage and liver function. If patients with sarcopenia are identified preoperatively, this gives the chance to adapt the intended operation. In these frail patients with sarcopenia it would for example be possible to leave more residual liver volume, or increase preoperatively the functional liver volume by portal vein embolisation or perform a two-stage hepatectomy. Perhaps treating malnutrition preoperatively in sarcopenic patients could also reduce the risks of liver surgery. If patients with sarcopenia are treated better and have a more “tailor made” approach, this will eventually lead to

less complications, shortening in length of hospital stay and better survival and therefore this may result in considerable cost-reduction. Collaboration and continuing to improve the aspects of preoperative assessment in patients undergoing liver resection will improve the quality of surgical care.

It is important that in the future every HPB-surgeon should have access to a Picture Archiving and Communication System *(*PACS) workstation and it would be valuable if HPB surgeons were able to use OsiriX® software. The validation of OsiriX® in this thesis made it possible to accelerate the development of liver volumetry in general on a personal computer but in the future this may perhaps also be applicable on mobile radiological wireless communication devices. Currently, not only in every day life but also in science the tablet computer and the smartphone are replacing the personal desktop computer step by step. The development of applications for mobile devices has exploded the last couple of years and the possibilities seem to be endless. It is already possible to run Osirix® on a tablet computer or even on a smartphone. Developments like this can help to better visualize and apprehend the anatomy of the liver pre- and intraoperatively. It can also be useful for training, teaching and performing safer surgical procedures.

There are still shortcomings in the currently freely downloadable volumetry software programs. In order to improve these programs we believe that medical scientists should work together with technical engineers. Medical doctors know best what the clinical problems are and engineers are best at finding the technical answer for these problems. Entrepreneurship will also be important for further implementation of liver volumetry. However, commercial software programmes do not often find their way into the clinic because they are expensive. High costs remain a problem because of reduced budgets in hospitals in the Netherlands as well as elsewhere in Europe. In the near future this will be an even bigger problem because of new cost-cutting political programs in healthcare. Another problem is that with the current infrastructure in science and business we have learned from the past that it will take at least six to seven years to distribute a new product (developed in a research project) on the market. This process can be enhanced and shortened through open innovation. Medical doctors, technicians and entrepreneurs should work together without barriers and such collaboration should be facilitated and promoted. Medical products like for instance liver volumetry software programmes should not be subject to copyright protection and should be in the public domain. ImageJ is a good example of a product like this. Its user community can, once the programme is in the public domain, further develop the software and solve any problems they encounter while using the software. When liver volumetry is further implemented in the workup of patients undergoing liver surgery, more patients can be operated and more complex liver resections can be performed safely. From a societal/economic point of view this is very important because in the Western world every year there are more and more patients with colorectal liver metastases in need of liver resection.

Ischemia-reperfusion injury

Ischemia-reperfusion injury is a pathophysiological phenomenon in a variety of diseases. Ischemia-reperfusion injury of the liver occurs frequently during liver resection when blood flow is occluded temporarily during liver resection to reduce blood loss [the so-called intermittent Pringle manoeuvre (IPM)]. To find new targets for therapy and characterize pathophysiological events during ischemia of the liver, the effect of the IPM was investigated. The results of the two studies on the IPM reported in this thesis underline that the rationale for the use of the IPM should be under discussion since it can lead to more hepatocellular damage and can even cause intestinal epithelial cell damage. More importantly, there is little evidence that applying IPM during routine liver resection is useful. The exact impact of IPM on routine liver resection warrants further evaluation. Some of the issues revealed in the studies in this thesis will help to understand the potential harmful effects of the IPM better. As a consequence it will be easier to make the right choice when to apply the IPM during liver surgery and when not. Optimizing surgical techniques like the IPM will eventually not only improve short- and long-term patients' outcome but also improve cost effectiveness. Optimizing these techniques will for example reduce costs of theatre time, hospital stay, and intensive care unit usage. Such cost-reduction is of great economical relevance in times of cut-backs on healthcare. Funding for research that focuses on the improvement of liver surgery techniques could translate into considerable savings to hospitals and health care programmes and this is therefore important for society.

Paracetamol and ophthalmate

The data of the thesis considering the relation between paracetamol (PCM), ophthalmate (OPH) and glutathione (GSH) have initiated a line of thought towards the development of a PCM tolerance test. This test would imply administering PCM and using OPH as an alternative readout for hepatic GSH to help predict liver failure post liver resection. A patent possibility was explored, but it was felt to be non-patentable by the University of Maastricht patentability agency. From a business point of view this test would be interesting since PCM is not an expensive drug and every year there will be more and more patients who could benefit from such a test. A PCM-test would be very useful for patients undergoing liver resection for benign or malignant tumours. These may be patients with an otherwise normal liver, or patients with underlying cirrhosis of the liver. Equally, it may be a helpful tool to test liver function in patients subjected to chemotherapy for cancer, because the chemotherapy may have serious adverse effects on the liver. Along the same lines, it may be a valuable test in patients undergoing liver transplantation, particularly for those involved in a living-related liver donation programme. Finally, it may be effective in titrating therapy in patients with PCM overdose, either accidentally or intentionally.

From a valorisation point of view this test was considered of interest since PCM is already FDA (Food and Drug Administration) approved and PCM is often used in standard care medicine. Therefore clinical trials would not be delayed by phase 1 and 2 studies and a potential PCM-test could be brought on the market faster compared to completely new substances. The described study in this thesis in which the biomarker OPH was tested after a PCM-challenge during liver surgery was innovative. In this study no inversely proportional increase in OPH was observed, related to the GSH drop after PCM-challenge. The data and set-up of this study are likely to be useful for future studies and experiments to eventually develop a PCM-test, which can demonstrate liver function capacity. We developed a method for pre-storage treatment of OPH samples and proposed also a LC-MS-MS method for accurately measuring OPH levels in human samples. This knowledge opens the door for new studies on the GSH-OPH pathway and creates opportunities. The developments described in this thesis can be important to perform liver surgery more safely in the future and will have a positive impact, in the first place for patients undergoing liver surgery, but also on society and on economy.